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Gentamicin in Hemodialyzed Critical Care Patients: Early Dialysis after Administration of a High Dose Should Be Considered

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Gentamicin is a widely used antibiotic in the intensive care unit (ICU). Its dosage is difficult to adapt to hemodialyzed ICU patients. The FDA-approved regimen consists of the administration of 1 to 1.7 mg/kg of gentamicin at the end of each dialysis session. Better pharmacokinetic management could be obtained if gentamicin were administered just before the dialysis session. We performed Monte Carlo simulations (MCS) to determine the best gentamicin pharmacokinetic profile (high peak and low trough concentrations). Then, 6 mg/kg of gentamicin was infused into 10 ICU patients over a period of 30 min. A 4-h-long hemodialysis session was started 30 min after the end of the infusion. Pharmacokinetic samples were regularly collected over 24 h. A one-compartment model with zero-order input and first-order elimination was developed in Nonmem version VI to analyze patients' measured gentamicin concentration-versus-time profiles. Finally, additional MCS were performed to compare the regimen chosen with the FDA-approved gentamicin regimen. High peak concentrations (C_{max}, 31.8 ± 16.8 mg/liter) were achieved. The estimated C_{24} and C_{48} values (concentrations 24 and 48 h, respectively, after the beginning of the infusion) were 4.1 ± 2.3 and 1.8 ± 1.2 mg/liter, respectively. The volume of distribution was 0.21 ± 0.06 liter/kg. MCS confirmed that the dosing regimen chosen achieved the target C_{max} whereas the FDA-approved regimen did not (31.0 ± 10.9 versus 8.8 ± 3.1 mg · liter^{-1}). Moreover, the C_{24} values were similar while the $AUC_{0\text{-}24}$ values were moderately increased (190.8 ± 65.0 versus 135 ± 42.2 mg · h · liter^{-1}). Therefore, administration of 6 mg/kg of gentamicin before hemodialysis to critically ill patients achieves a high C_{max} and an acceptable AUC, maximizing pharmacokinetic/pharmacodynamic endpoints.

Severe sepsis and septic shock are major causes of morbidity and mortality in the intensive care unit (ICU) (1). Early and appropriate infection control is a priority in sepsis management of critically ill patients to improve outcome (2, 3) and requires optimal use of antibiotics. This goal can be achieved by using the pharmacokinetic/pharmacodynamic (PK/PD) properties of antibiotics in order to maximize their therapeutic potential and minimize toxicity (4–6).

Aminoglycosides (AG) demonstrate concentration-dependent killing of both Gram-positive and Gram-negative bacteria, with rapid bactericidal activity (7). Combination therapy with AG, especially gentamicin, is widely recommended for the treatment of severe infections in order to increase the chance of adequate empirical therapy (8). Several recent studies have shown improved outcomes in patients with either shock or Gram-negative bacillary bacteremia treated with a combination of AG and β-lactams, which interact synergistically (9, 10). AG efficiency is related to the peak AG concentration (C_{max}) (11, 12), whereas AG-associated toxicities (cochleovestibular toxicity and nephrotoxicity) are related to body exposure as measured by the area under the concentration-time curve (AUC) and trough concentrations (13, 14). For several years, data in the literature have suggested that a once-daily dosing regimen is as effective as the conventional multiple daily dosing regimen but reduces toxicity associated with AG therapy (15). Monitoring of AG concentrations facilitates appropriate dosing in order to prevent underdosing and therapeutic failure, as well as overdosing and toxicity (16–18). However, many antibiotic regimens that have been developed for noncritically ill patients are likely to be inappropriate in the ICU population (19). The AG dosage is difficult to adapt to ICU patients because of the PK changes observed in these patients induced especially by the frequent use of extracorporeal therapies, such as renal replacement therapies (19, 20). AG have a low molecular weight and a low affinity for plasma protein, allowing them to be easily removed by dialysis (18). The FDA-approved regimen for adults undergoing hemodialysis consists of the administration of 1 to 1.7 mg/kg of gentamicin at the end of each dialysis period. However, theoretical considerations and emerging clinical data suggest that this may not be the most beneficial strategy (21). Results of the studies conducted with patients with chronic kidney disease requiring dialysis suggest a better PK management if an AG is administered just before the dialysis session (22–24). We therefore hypothesize that the administration of a high dose of gentamicin to critically ill hemodialyzed patients just prior to intermittent hemodialysis (IHD) would allow high peak concentrations, maximizing bacterial killing, and rapid removal by the subsequent dialytic clearance, minimizing total exposure (AUC) and toxicity.

PK/PD studies of ill patients, in particular, ICU patients, are limited by the large spectrum of pathologies that influence PK, as well as by the limited number of patients available for inclusion. PK modeling and Monte Carlo simulations (MCS) are commonly used as decision support tools to guide dosing selection. Briefly, MCS use central tendency and dispersion of PK parameters in order to generate more realistic concentration-time profiles.

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Therefore, the application of MCS should be considered a valuable technique in the ICU setting (25).

The purpose of this clinical investigation was to determine the best gentamicin dosing strategy (allowing the best benefit/risk ratio) in ICU patients requiring IHD. The study protocol was sequentially implemented by using (i) preliminary MCS using literature data in order to determine the best dosing regimen based on the PK profile, (ii) administration of gentamicin to patients according to the regimen chosen from preliminary MCS, (iii) fitting of the developed population PK model to our data, and (iv) comparison of the dosing regimen chosen to the usual FDA-approved regimen with additional MCS using the population PK parameters estimated for our patients.

MATERIALS AND METHODS

Experimental design. This was a prospective, monocentric, observational study performed in the medical ICU of our hospital. The study protocol was approved by the French Society for Critical Care ethics committee, which waived the need for informed consent but required that an informational letter be given to each patient or a relative. Ten consecutive adult intensive care patients with acute kidney injury needing IHD and suffering from a nosocomial or community-acquired infection requiring treatment with gentamicin were included. They were excluded if pregnant, if they had endocarditis, or if they had received gentamicin in the last 7 days.

The data collected included: demographic and morphometric data, diagnosis on admission, past medical history, SOFA (sequential organ failure assessment) (26), and SAPS II (simplified acute physiology score II) (27) values, hemodynamic and respiratory status on inclusion, site of infection, associated antibiotics, and IHD parameters. Positive microbiological cultures were recorded, as were the MICs for the identified pathogens, when available.

Gentamicin (6 mg/kg, based on actual body weight; Schering-Plough SAS) was infused intravenously over a period of 30 min with a syringe pump. IHD was performed with an AK 200 Ultra S machine (Gambro Inc.). All subjects were dialyzed according to a standardized method with a polymethylmethacrylate dialyzer (Toray B3; Toray Medical Co.). The dialysis treatment was 4 h long. The blood flow rate was kept constant between 200 and 300 ml/min. The IHD session was started 30 min after the end of the infusion.

This experimental design was chosen according to preliminary MCS of drug concentration-time curves determined in order to choose adequate dosing and hemodialysis parameters for future experiments. MCS of different weight-based dosing regimens with a differential delay between gentamicin infusion and the start of a 4 h-hemodialysis session were undertaken with a PK model previously developed to describe gentamicin concentration-time curves (24) (Nonmem version VI; ICON Development Solutions, Ellicott City, MD). There is no consensus on modifications of the volume of distribution (V) in ICU patients, probably because of the high heterogeneity of patients admitted to ICUs (28). Therefore, a standard V of 0.25 liter/kg was chosen (29). Similarly no data were available for hemodialyzed ICU patients; therefore, values for interdialytic or nonhemodialysis clearance (CL_{NHD}), hemodialysis clearance (CL_{HD}), and random parameters were obtained from a previous population PK study of patients with end-stage renal disease (24), assuming a 70-kg patient (i.e., $CL_{NHD} = 0.00554$ liter $\cdot$ h^{-1} $\cdot$ kg^{-1} and $CL_{HD} = 0.068$ liter $\cdot$ h^{-1} $\cdot$ kg^{-1}). Regimens with different doses of gentamicin (1.5, 6, and 10 mg/kg of body weight) administered (i) at the beginning of the hemodialysis session (dialysis during administration), (ii) 1 h before hemodialysis commenced (dialysis just after administration, during the early phase of disposition), or (iii) 20 h before hemodialysis commenced (dialysis during the last 4 h of disposition) were assessed (Table 1). Each MCS generated concentration-time profiles for 1,000 subjects per regimen, allowing realistic estimates of the C_{max}, $AUC_{0\text{-}24}$ (area under the concentration curve from 0 to 24 h), and C_{24} (concentration 24 h after the beginning of the infusion). The abilities of the regimens to achieve a high C_{max} with a low $AUC_{0\text{-}24}$ were then compared (30). Actually, as demonstrated by previous PK/PD analysis, the efficiency of gentamicin requires a peak concentration 10-fold higher than the MIC, whereas the toxicity of gentamicin has been related to trough concentrations of >2 mg/liter (12, 31). Since the AUC represents the total exposure to a drug, the AUC could be a useful parameter to evaluate gentamicin toxicity (30) and efficacy (using the AUC/MIC ratio) (17).

TABLE 1 Simulated C_{max}, $AUC_{0\text{-}24}$, and C_{24} after MCS of 1.5, 6, and 10 mg/kg of gentamicin infused at the beginning of the dialysis session and 1 and 20 h before the dialysis session

Time of gentamicin infusion and gentamicin dose (mg/kg)	Mean C_{max} (mg $\cdot$ liter^{-1}) $\pm$ SD	Mean $AUC_{0\text{-}24}$ (mg $\cdot$ h $\cdot$ liter^{-1}) $\pm$ SD	Mean C_{24} (mg $\cdot$ liter^{-1}) $\pm$ SD
Beginning of dialysis			
1.5	4.8 ± 0.9	43.8 ± 6.1	1.2 ± 0.4
6	19.5 ± 3.4	173.9 ± 25.9	4.7 ± 1.7
10	31.9 ± 5.8	292.1 ± 41.0	8.1 ± 2.7
1 h before			
1.5	6.1 ± 1.4	44.5 ± 6.1	1.1 ± 0.4
6	24.3 ± 5.4	177.9 ± 24.3	4.4 ± 1.6
10	40.4 ± 9.1	296.6 ± 40.6	7.3 ± 2.6
20 h before			
1.5	6.1 ± 1.4	103.5 ± 24.7	1.1 ± 0.4
6	24.3 ± 5.6	414.0 ± 98.6	4.4 ± 1.6
10	40.4 ± 9.4	690.0 ± 164.3	7.4 ± 2.7

PK sampling and gentamicin assay. Blood samples were drawn without anticoagulant at 1 (C_{max}), 6, 12, and 20 h after the start of infusion and every 12 h until concentrations of <2 mg/liter were attained. Serum was collected and assayed within 1 h in the pharmacokinetics laboratory of our hospital. Measurements of gentamicin concentrations were performed by a cloned enzyme donor immunoassay (CEDIA; Microgenics, Thermo Scientific, Villeurbanne, France) on a modular analyzer (Roche Diagnostics, Meylan, France). The lower limit of quantification was 0.24 μg/ml, and between-run imprecision ranged between 2.1 and 4.0%.

Population PK modeling. A one-compartment model with zero-order input and first-order elimination was developed in Nonmem version VI (ICON Development Solutions, Ellicott City, MD) in order to analyze patients' gentamicin concentration-versus-time profiles. The model was parameterized in terms of CL_{NHD}, CL_{HD}, and V as follows: $dC/dt = R_0/V - [(CL_{HD} + CL_{HD})/V] \times C$, where R_0 is the rate of infusion and C is the serum drug concentration.

The model was fitted to data obtained from patients by the first-order conditional estimation method with the interaction option. The interindividual variability (η) was described by an exponential model. The residual variability (ε) was described by an additive, a proportional, or a combined proportional and additive error model. Both one- and two-compartment models with zero-order input and first-order elimination were tested. Model fit was evaluated by considering the value of the objective function, parameter estimates, their between-subject variability, and visual inspection of goodness-of-fit plots, including observed and predicted concentrations versus time, observations versus population predictions and versus individual predictions, and weighted residuals versus time and versus predicted concentrations. Validation of the final model also included a visual predictive check (VPC) (32).

The population PK model was used to estimate gentamicin C_{24}, C_{48}, and $AUC_{0\text{-}24}$ values for each patient. When the MIC was available, the C_{max}/MIC and $AUC_{0\text{-}24}$/MIC ratios were calculated.

After completion of the experimental study, additional MCS were performed in order to compare the dosing regimen chosen to the usual FDA-

TABLE 2 Characteristics of patients and of infections treated on inclusion

Patient no.	BMI[a] (kg/m^2)	SAPS II value	SOFA value	Pressor amines	MV[b]	Type of infection[c]	Microbiological culture	MIC (mg/liter)	Associated antibiotic(s)
1	29.1	53	12	Yes	Yes	Fasciitis (c)	Negative		Piperacillin-tazobactam
2	28.6	46	15	Yes	Yes	Angiocholitis (c)	*Escherichia coli*	2	Amoxicillin, levofloxacin
3	22.2	51	4	No	No	Pyelonephritis (c)	*Serratia marcescens*	1	Ceftriaxone
4	19.7	65	9	Yes	Yes	VAP (n)	MSSA[d]	0.5	Piperacillin-tazobactam, vancomycin
5	21.8	48	13	Yes	Yes	Peritonitis (c)	Negative		Ceftriaxone, metronidazole
6	19.5	34	6	Yes	Yes	VAP (n)	*Pseudomonas aeruginosa*	NA[e]	Piperacillin-tazobactam
7	28.7	49	13	Yes	Yes	Mediastinitis (n)	*Escherichia coli*	1	Piperacillin-tazobactam
8	33.3	47	7	Yes	Yes	Lower-limb ischemia (n)	*Enterococcus faecium*	NA	Piperacillin-tazobactam, teicoplanin
9	29.8	38	3	No	No	Pyelonephritis (c)	*Escherichia coli*	1	Ceftriaxone
10	29.6	59	13	Yes	Yes	Septic thrombophlebitis (n)	MSSA	0.5	Oxacillin
Mean ± SD	26.2 ± 4.9	49 ± 11	9.5 ± 4.3						

[a] BMI, body mass index.
[b] MV, mechanical ventilation.
[c] n, nosocomial; c, community acquired; VAP, ventilation-associated pneumonia.
[d] MSSA, methicillin-susceptible *Staphylococcus aureus*.
[e] NA, not available.

approved regimen, i.e., a loading dose of 1.7 mg/kg after hemodialysis. The latter simulations were performed by using population PK parameters obtained from patients in this study.

RESULTS

Patients' characteristics. All 10 patients completed the study. All of them were male; on admission, their mean age was of 64.5 ± 10.1 years and their mean weight was 72.7 ± 16.4 kg. Their body mass indexes are shown in Table 2. Each patient's hemodynamic and ventilatory status and ICU severity scores on inclusion are displayed in Table 2, as is the site of infection, results of microbiological cultures, the MICs for the pathogens, and antibiotic combinations. Dialysis sessions were consistent with the prescription in most cases; the mean blood flow was 283 ± 20 ml/min, and the mean hemodialysis session length was 236 ± 13 min.

Measured gentamicin concentrations. Table 3 reports the measured gentamicin C_{max} for each patient. Optimal C_{max}/MIC and $AUC_{0\text{-}24}$/MIC ratios were successfully achieved by using our experimental design.

Population PK/PD analysis. A zero-order input one-compartment model and a proportional-error model provided the best fit to the data and were chosen as the best models. A two-compartment model did not improve the fit, since the reduction in the objective function was not significant. Similarly, including weight or ideal body weight in the model combined as factors influencing V did not improve the model fit. The parameters of the final model are reported in Table 4. Parameter uncertainty was expressed as the relative standard error of estimates (RSE) and was small for fixed-effect parameters (12 to 16%) and higher for random-effect parameters (38 to 59%). Basic goodness-of-fit plots for the final model did not reveal obvious model misspecification;

TABLE 3 Actual body weight, gentamicin dosing, gentamicin C_{max} measurement, and main PK parameters[a] estimated for each patient after gentamicin administration

Patient no.	Actual body wt (kg)	Gentamicin dose (mg)	C_{max} (mg/liter)	C_{max}/MIC	V (liter/kg)	CL_{HD} (ml/min)	CL_{NHD} (ml/min)	$AUC_{0\text{-}24}$ (mg.h/liter)	$AUC_{0\text{-}24}$/MIC	C_{24} (mg/liter)	C_{48} (mg/liter)
1	93.5	560	29.1		0.19453	82.4	18.7	176		2.39	0.54
2	80	500	21.8	10.9	0.26541	92.6	16.3	155	77.5	2.76	0.91
3	62	380	24.1	24.1	0.25076	53.9	5.8	230	230	6.25	3.66
4	60	360	43	86	0.14139	61.8	6.2	214	428	3.54	1.23
5	63	360	22.3		0.24882	70.9	7.4	168		3.87	1.97
6	54.5	300	18.5	NA[b]	0.28045	100.3	6.8	107	NA	2.16	1.14
7	83	500	75.1	75.1	0.08667	31.1	4.7	485	485	9.62	3.73
8	102	600	25.9	NA	0.22503	102.5	10	200	NA	4.81	2.57
9	86	520	24.3	24.3	0.22307	57.5	22.7	185	185	2.45	0.45
10	72	430	34.1	68.2	0.17777	94.2	5.4	165	330	3.13	1.70
Mean ± SD	75.6 ± 15.8	451 ± 99	31.8 ± 16.8	48.1 ± 31.9	0.209 ± 0.060	76.5 ± 23.1	10.4 ± 6.4	209 ± 103	289.3 ± 153.9	4.1 ± 2.3	1.8 ± 1.2

[a] All predicted PK parameter values were obtained by using the population PK model developed.
[b] NA, data not available.

TABLE 4 PK parameter values estimated with the population PK model

Parameter	Model estimate	RSE (%)
PK parameters		
CL_{NHD}	0.1205[a]	16
CL_{HD}	0.955[a]	14
V	0.201[b]	12
Interindividual variability[a]		
CL_{NHD}	48[c]	38
CL_{HD}	41[c]	56
V	35[c]	59
Residual variability (proportional error)	11[c]	40

[a] Milliliters per minute per kilogram.
[b] Liters per kilogram.
[c] Coefficient of variation (percent).

plots of observations versus population predictions and versus individual predictions (Fig. 1a) show random variation around the line of unity, and plots of weighted residuals show random variation centered around zero with no systematic trend (Fig. 1b). The PK model developed adequately describes the concentration-time profile of gentamicin in our patients (Fig. 1c). The VPC plot demonstrated that model predictions were in agreement with the observed data. Less than 10% of observed concentrations were outside the 90% VPC interval. Table 3 shows individual PK parameters estimated for the patients enrolled (V, C_{24}, C_{48}, $AUC_{0\text{-}24}$, CL_{HD}, and CL_{NHD}).

TABLE 5 Simulated C_{max}, $AUC_{0\text{-}24}$, and C_{24} after MCS of a 6-mg/kg dose of gentamicin infused 1 h before hemodialysis and of a 1.7-mg/kg dose at the end of the hemodialysis session

Treatment	Mean C_{max} ($mg \cdot liter^{-1}$) ± SD	Mean $AUC_{0\text{-}24}$ ($mg \cdot h \cdot liter^{-1}$) ± SD
6 mg/kg 1 h before hemodialysis	31.0 ± 10.9	190.8 ± 65
1.7 mg/kg at end of dialysis session	8.8 ± 3.1	135.0 ± 42.2

Comparison of regimen chosen and FDA-approved regimen. MCS performed with population PK parameters estimated from our patients confirmed that the dosing regimen chosen achieves the target C_{max} whereas the FDA-approved regimen does not. Moreover, the C_{24} values were quite similar while the AUCs were moderately increased (Table 5).

DISCUSSION

Sepsis is one of the most common causes of death in critically ill patients, so optimization of antibiotic dosing is critical. In patients receiving IHD, PK parameters may be affected by critical illness and IHD itself; therefore, appropriate drug doses can be difficult to determine. This is the first study of critically ill patients aiming to improve the efficacy-toxicity profile of gentamicin when patients require IHD.

In our study, the most suitable gentamicin dosage defined from preliminary PK simulations consisted of a gentamicin infu-

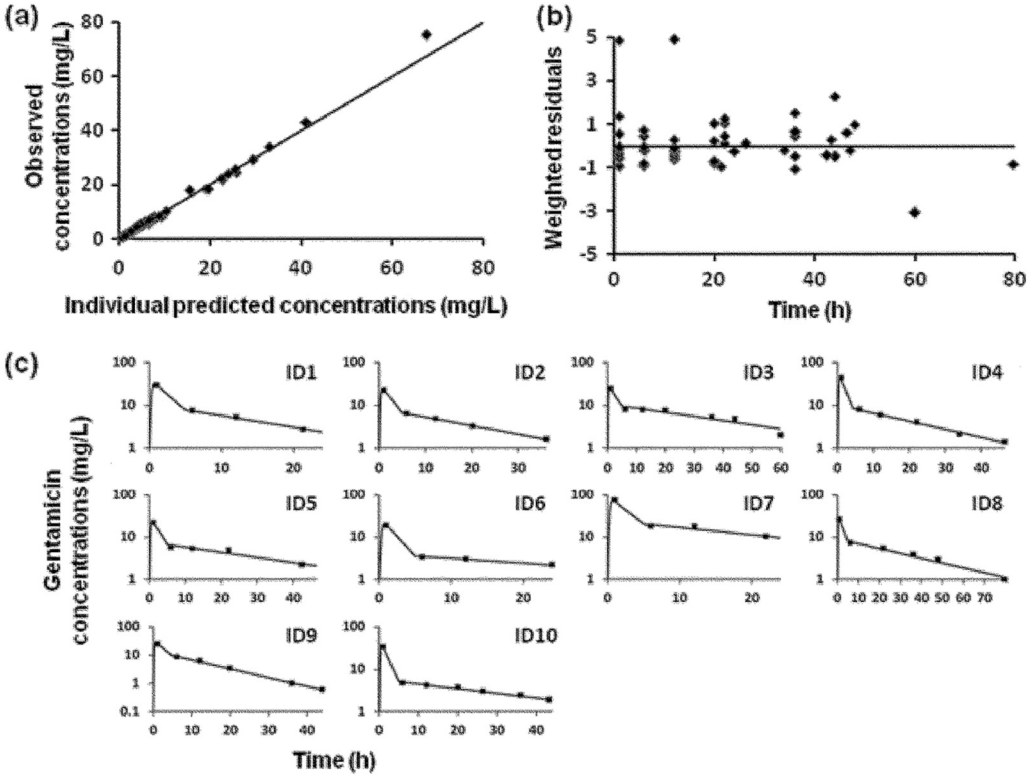

FIG 1 Goodness-of-fit plots for the final population PK model. (a) Observed concentrations versus individual predicted concentrations. The line $x = y$ is the identity line. (b) Weighted residuals versus time. (c) Gentamicin concentration-versus-time profiles of the patients enrolled in this study (ID1 to ID10). Each black square represents a measured concentration. The line represents the individual estimate from the final population PK model.

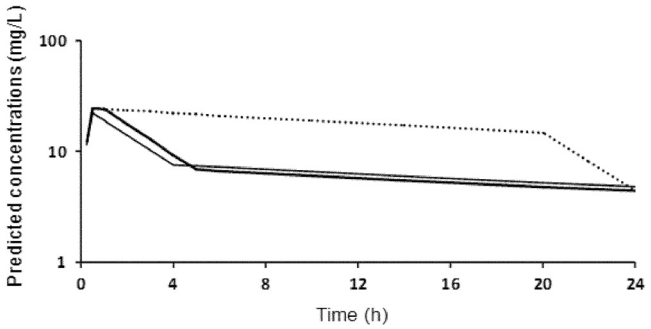

FIG 2 Simulated gentamicin concentrations versus time for a 6-mg/kg dose administered at the beginning of the hemodialysis session (thin line) or at 1 h (bold line) or 20 h (dotted line) before hemodialysis commenced.

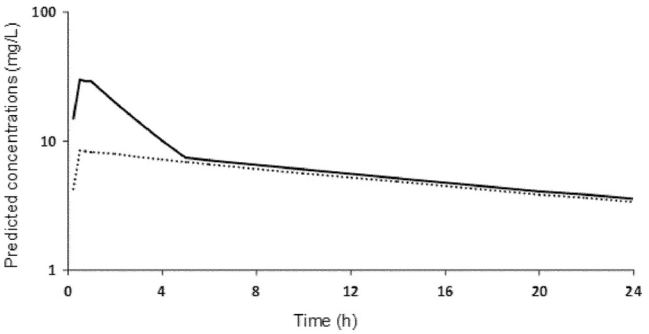

FIG 3 Simulated gentamicin concentrations versus time for a 6-mg/kg dose administered at the beginning of the hemodialysis session (bold line) and for a 1.7-mg/kg dose (dotted line) administered at the end of the hemodialysis period.

sion of 6 mg/kg over a period of 30 min, starting 1 h before the beginning of a 4-h-long IHD session. Administration of the dose just prior to IHD allowed for high peak concentrations, followed by rapid removal, suggesting better efficiency and less toxicity. This regimen used the lowest dose that achieved the target C_{max}.

This gentamicin dosing regimen was administered to 10 ICU patients. The C_{max} values observed were higher than those obtained by preliminary simulations and exceed 20 mg/liter in all cases except one, implying adequate efficacy against most infections. An adequate ratio of C_{max} to the bacterial gentamicin MIC was always achieved, considering local bacterial ecology. Since the C_{max} value may depend upon sampling conditions (33), the AUC_{0-24}/MIC ratio was also estimated for each patient when the MIC was available. The estimated V in our population was not increased, in contrast to previous studies (28, 34, 35), despite the severity status of the patients enrolled, demonstrated by the high-severity SOFA and SAPS II score values. This result confirms the importance of PK variability in ICU patients due to critical illness itself, the use of extracorporeal therapies, the course of the infection, etc. (18, 36). Regarding the risk of AG-induced toxicity, as gentamicin clearance is reduced in hemodialyzed patients, C_{24} values were significantly higher than the recommended threshold at 24 h (30), requiring a longer dosage interval. In most of cases, the estimated C_{48} values were lower than 2 mg/liter, allowing a second gentamicin injection at 48 h, as in the study conducted by Roberts et al. (37). Besides, in patients receiving IHD, the trough concentration is probably a poor marker of AG toxicity. Indeed, the same trough concentrations achieved may correspond to different AUCs, depending on the dialysis period chosen (Fig. 2). The mean AUC_{0-24} calculated in our study was also higher than the AUC_{0-24} values (70 to 120 mg · h/liter) recommended by others (24, 30). But the target C_{max} in these studies (10 mg/liter) did not guarantee adequate efficacy against severe infections. The clinical significance of the increased AUCs with the proposed 6-mg/kg regimen was not assessed in our study and is unknown. A high AUC could correspond to AG toxicity but could be preferable to achieve a higher C_{max} to maximize bacterial killing and prevent bacterial resistance. All of the PK targets cannot be reached easily simultaneously in ICU patients because of the wide PK variability of AG in these patients, especially in those receiving IHD. This highlights the need to monitor serum AG concentrations in order to optimize the PK/PD targets.

Additional MCS were performed to compare the potential benefits of this new regimen to those of the usual gentamicin regimen. As Fig. 3 shows, the proposed schedule allows the achievement of a high C_{max} while the FDA-approved regimen does not. Even if the AUC_{0-24} is increased by using our schedule, the trough concentrations are similar to those of the FDA-approved regimen. In this way, with our schedule, high gentamicin concentrations are obtained over a short period of time, potentially minimizing the risk of toxicity according to saturable uptake kinetics of gentamicin in cells (38). This administration schedule outperforms the usually recommended regimen.

This study also highlights the interest of using MCS to support the experimental design of studies of critically ill patients; the use of a data maximization strategy should be considered a highly valuable method to improve the antibiotic administration schedule for this type of patient (25).

Nevertheless, this study has some limitations. The PK profile of gentamicin was evaluated only during the first 48 h after administration, and thus, no conclusions can be drawn concerning the PK profile of subsequent doses. In addition, further experiments are necessary to confirm the clinical and microbiological efficacy and safety of such a gentamicin regimen.

Conclusion. The results of this study support the hypothesis that the achievement of a 4-h-long hemodialysis session, started 30 min after the infusion of a high dose of an AG (6 mg/kg of gentamicin) should be considered for infected critical care patients receiving IHD. Prehemodialysis AG infusion maximizes PK/PD endpoints, and the FDA-approved regimen does not.

This study demonstrates how to optimize gentamicin PK-PD parameters in patients receiving IHD; however, studies assessing the clinical efficiency and demonstrating the absence of toxicity of such a gentamicin regimen should be performed.

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